

Synthesis, Characterization and Antimicrobial Activity of N-(5-(4-(methylsulfonyl) benzyl)-1, 3, 4-thiadiazol-2-yl)-1-Phenylmethanimine Promoted by MSA

M.N. V. Sarat¹, Ch.Jyothi¹, Dr.N.Krishnarao^{1*},

^{1*}.Department of organic chemistry, PRISM PG&DG College (Affiliated to Andhra University),
Visakhapatnam, India, 530016

Corresponding Author Email.ID: naallakrishnarao@gmail.com

ABSTRACT:

Schiff bases are multipurpose ligands that are created when primary amines condense with carbonyl groups. N-(5-(4-(methylsulfonyl) benzyl)-1, 3, 4-thiadiazol-2-yl) Synthesis MSA promotes -1-phenylmethanimine, which is available When ethanol and acetic acid reflux, 5-(4-(methylsulfonyl) benzyl)-1, 3, 4-thiadiazol-2-amine reacts with aromatic aldehyde. 2-(4-(methylsulfonyl) phenyl) acetic acid and thiosemicarbaide in con H_3PO_4 in DMF as solvent at 750C can be converted to the chemical 5-(4-(methylsulfonyl) benzyl)-1, 3, 4-thiadiazol-2-amine. All of the mentioned analogous were assessed using sophisticated spectroscopic techniques such 1H NMR, ^{13}C NMR, and LCMS, and elemental analysis was used to determine their structural makeup. Additionally, the antimicrobial activity of the newly synthesized compounds was evaluated.

KEYWORDS:

5-(4-(methylsulfonyl) benzyl)-1, thiosemicarbaide, substituted aryl aldehyde, Schiff's base, MSA, bioevluation.

1. INTRODUCTION:

Compounds containing an azomethine group ($-CH=N-$), known as Schiff bases are formed by the condensation of a primary amine with a carbonyl compound. Schiff bases of aliphatic aldehydes are relatively unstable and are readily polymerizable while those of aromatic aldehydes, having an effective conjugation system, are more stable. Schiff bases have number of applications viz., preparative use, identification, detection and determination of aldehydes or ketones, purification of carbonyl or amino compounds, or protection of these groups during complex or sensitive reactions. They also form basic units in certain dyes. In organic synthesis, Schiff base reactions are useful in making carbon-nitrogen bonds

Schiff bases appear to be an important intermediate in a number of enzymatic reactions involving interaction of an enzyme with an amino or a carbonyl group of the substrate One of the most important types

of catalytic mechanism is the biochemical process which involves the condensation of a primary amine in an enzyme usually that of a lysine residue, with a carbonyl group of the substrate to form imine, or Schiff base.

Schiff bases and azo Schiff bases important intermediates for the synthesis of some application such as biological activity[2-4], clinical[5,6], analytical[7,8], Anticancer[9,10] and catalytical[11,12] Azo Schiff base compounds are highly important well known and widely used substances in textile, paper and coloring agents for foods and cosmetics industries[13,14], Azo Schiff base and their complexes with transition metal ions are also of importance due to their complexing, catalytically, biological properties[15,16].and corrosion inhabitation in acid media[17,18],

Our attention was on the more recent, undocumented synthesis pathways for these condensed molecules. We have assessed the newly synthesized compounds' antibacterial of our earlier lab studies. Initially, we attempted a pilot reaction using substituted aromatic aldehydes, 5-(4-(methylsulfonyl) benzyl)-1, 3, 4-thiadiazol-2-amine in the presence P-Toluene Sulphonic acid in ethanol to the RB flask. The reaction was carried on magnetic stirrer at RT (Scheme-I).

2. METHODS AND MATERIALS:

2.1. EXPERIMENTAL:

All the chemicals, synthetic reagents, and solvents were procured from commercially and they were used without further purification. The standard procedures were used to follow by dry solvents and the reaction mixture were checked by thin-layer chromatography (n-hexane: Ethylacetate) on silica gel plates coated with alumina. The melting points of the desired compounds were determined in open capillary tubes and were uncorrected. ¹H NMR and ¹³C-NMR spectrum were recorded titled derivatives on a Bruker DRX-400MHz and 100MHz instrument using CDCl₃ as a solvent. The chemical shifts, δ , are given in ppm downfield and upfield from the internal standard Tetramethylsilanes. The splitting patterns titled compounds are designated as follows; s: singlet; d: doublet and m: multiplet. The mass spectra were obtained on a Shimadzu 2010A LCMS spectrometer. Elemental analysis of the derivatives was recorded by the instrument.

2.2. General preparation of 5-(4-(methylsulfonyl) benzyl)-1, 3, 4-thiadiazol-2-amine:

The mixture of the 2-(4-(methylsulfonyl) phenyl) acetic acid and thiosemicarbazide taken in in con H₂SO₄ in DMF as solvent at 70-80⁰C. The reaction carried on magnetic stirrer at RT. A catalytic amount of P-toluene sulphonic acid added to the above mixture. The reaction was monitored after all the reactants are consumed during the reaction time, after completion of the reaction, cold water added to the product. The product can be

washed with brine solution and solid product was separated out. We desired compound can be recrystallized from ethanol.

Pale yellow solid ; Yield-92%; m.p $-151-153^{\circ}\text{C}$; ^1H NMR (400MHz, CDCl_3) δ in ppm: 7.754-7.510(m,4H,Ar-H),6.128(s,2H,NH₂),3.458(s,2H,-CH₂-),2.417(s,3H,CH₃). ^{13}C NMR(100 MHz , CDCl_3) δ in ppm:162.08, 160.21, 140.08,133.54,128.57,128.12, 45.33, 37.05; . LCMS (m/z):269.74 (M⁺).Molecular formulas: C₁₀H₁₁N₃O₂S₂.Elemental analysis: Calculated:C-44.59,H-4.12,N-15.60. Obtained: C-44.52,H-4.10,N-15.69.

2.3. General preparation of N-(5-(4-(methylsulfonyl) benzyl)-1, 3, 4-thiadiazol-2-yl)-1-phenyl methanimine:

5-(4-(methylsulfonyl) benzyl)-1, 3, 4-thiadiazol-2-amine (1mmol) introduced in 100 ml RB flask in ethanol and substituted aryl aldehyde (1mmol) added to the RB flask. The reaction was carried on magnetic stirrer at RT. A catalytic amount of P-Toluene Sulphonic acid added to the above mixture. The reaction was monitored after all the reactants are consumed during the reaction time, after completion of the reaction, cold water added to the product. The product can be washed with brine solution and solid product was separated out. We desired compound can be recrystallized from ethanol.

2.3.1. N-(5-(4-(methylsulfonyl) benzyl)-1, 3, 4-thiadiazol-2-yl)-1-phenyl methanimine (4a) :

White solid, Yield-87%; m.p $-169-171^{\circ}\text{C}$; ^1H NMR (400MHz, CDCl_3) δ in ppm: 8.846 (s, 1H, =CH-), 7.712-7.484(m, 9H, Ar-H), 3.124 (s, 2H, -CH₂-), 2.425(s, 3H,-CH₃); ^{13}C NMR (100MHz, CDCl_3) δ in ppm: 160.28, 158.74, 140.69, 134.62, 132.56, 130.45, 129.62, 129.26, 128.77, 128.16, 46.65, 36.16; LCMS (m/z): 357.06 (M⁺);. Molecular formula: C₁₇H₁₅N₂O₂S₂; Elemental analysis: Calculated: C-57.12,H-4.23,N-11.76.Obtained: C-57.06,H-4.21,N-11.82.

2.3.2..4-(((5-(4-(methylsulfonyl)benzyl)-1,3,4-thiadiazol-2-yl)imino)methyl)phenol(4b) :

White solid, Yield-88%; m.p $-175-177^{\circ}\text{C}$; ^1H NMR (400MHz, CDCl_3) δ in ppm: 9.562(s,1H,-OH), 8.745 (s, 1H, =CH-), 7.746-7.496(m, 6H, Ar-H), 6.942-6.816(m,2H,Ar-H),3.356 (s, 2H, -CH₂-), 2.657(s, 3H,-CH₃); ^{13}C NMR (100MHz, CDCl_3) δ in ppm;160.67, 157.38, 155.82, 140.25, 134.61, 130.46, 129.59, 129.04, 128.72, 127.33, 46.48, 35.65; LCMS (m/z): 374.21 (M+H);. Molecular formula: C₁₇H₁₅N₂O₃S₂; Elemental analysis: Calculated: C-54.68,H-4.05,N-12.25.Obtained: C-54.61,H-4.03,N-12.32.

2.3.3.1-(3,4-dimethoxyphenyl)-N-(5-(4-(methylsulfonyl)benzyl)-1,3,4-thiadiazol-2-yl) methanimine (4c):

White solid, Yield-90%; m.p – 194-196⁰C; ¹HNMR (400MHz, CDCl₃) δ in ppm: 8.814 (s, 1H, =CH-), 7.615-7.423(m, 7H, Ar-H), 3.794 (s, 3H, -OCH₃-), 3.594 (s, 3H, -OCH₃), 3.145 (s, 2H, -CH₂), 2.341(s, 3H, -CH₃); ¹³CNMR (100MHz, CDCl₃) δ in ppm; 160.67, 157.38, 155.82, 140.25, 134.61, 130.46, 129.59, 129.04, 128.72, 127.33, 46.48, 35.65; LCMS (m/z): 418.72 (M+2);. Molecular formula: C₁₉H₁₉N₃O₄S₂; Elemental analysis: Calculated: C-54.66, H-4.59, N-10.06. Obtained: C-54.60, H-4.57, N-10.11.

2.3.4.(Z)-1-(4-chlorophenyl)-N-(5-(4-(methylsulfonyl)benzyl)-1,3,4-thiadiazol-2-yl) methanimine (4d):

Light yellow solid, Yield-87%; m.p – 201-203⁰C; ¹HNMR (400MHz, CDCl₃) δ in ppm: 8.917 (s, 1H, =CH-), 7.714-7.496(m, 8H, Ar-H), 3.615 (s, 2H, -CH₂), 2.562(s, 3H, -CH₃); ¹³CNMR (100MHz, CDCl₃) δ in ppm; 161.74, 159.09, 141.26, 136.15, 133.09, 130.41, 129.84, 129.25, 128.64, 128.28, 45.62, 34.33; LCMS (m/z): 393.28 (M+2);. Molecular formula: C₁₇H₁₄ClN₃O₂S₂; Elemental analysis: Calculated: C-52.10, H-3.60, N-10.72. Obtained: C-52.02, H-3.58, N-10.78.

2.3.5. (Z)-1-(4-bromophenyl)-N-(5-(4-(methylsulfonyl)benzyl)-1,3,4-thiadiazol-2-yl) methanimine (4e) :

Red compound, Yield-88%; m.p – 210-212⁰C; ¹HNMR (400MHz, CDCl₃) δ in ppm: 8.856 (s, 1H, =CH-), 7.745-7.325(m, 8H, Ar-H), 3.568 (s, 2H, -CH₂), 2.574(s, 3H, -CH₃); ¹³CNMR (100MHz, CDCl₃) δ in ppm; 161.94, 160.62, 141.38, 134.35, 132.06, 130.84, 129.54, 128.15, 45.68, 36.12; LCMS (m/z): 436.46(M+2);. Molecular formula: C₁₇H₁₄BrN₃O₂S₂; Elemental analysis: Calculated: C-46.80, H-3.23, N-9.63. Obtained: C-46.73, H-3.321, N-9.70.

2.3.6.(Z)-4-(((5-(4-(methylsulfonyl)benzyl)-1,3,4-thiadiazol-2-yl)imino)methyl) benzonitrile(4f):

Pale red compound, Yield-85%; m.p – 215-216⁰C; ¹HNMR (400MHz, CDCl₃) δ in ppm: 8.674 (s, 1H, =CH-), 7.845-7.512(m, 8H, Ar-H), 3.665 (s, 2H, -CH₂), 2.562(s, 3H, -CH₃); ¹³CNMR (100MHz, CDCl₃) δ in ppm; 161.74, 160.65, 141.26, 138.35, 131.56, 129.64, 128.66, 128.25, 127.38, 118.57, 116.57, 45.96, 37.62; LCMS (m/z): 383.37(M+);. Molecular formula: C₁₈H₁₄N₄O₂S₂; Elemental analysis: Calculated: C-56.53, H-3.69, N-14.55. Obtained: C-56.46, H-3.67, N-14.62.

2.3.7.(Z)-N-(5-(4-(methylsulfonyl) benzyl)-1,3,4-thiadiazol-2-yl)-1-(4-nitrophenyl) methanimine(4g)

Red solid, Yield-85%; m.p – 195-197⁰C; ¹HNMR (400MHz, CDCl₃) δ in ppm: 8.914 (s, 1H, =CH-), 8.310-7.615(m, 8H, Ar-H), 3.676 (s, 2H, -CH₂), 2.475(s, 3H, -CH₃); ¹³CNMR (100MHz, CDCl₃) δ in ppm; 162.66, 160.24, 149.32, 140.72, 138.90, 131.67, 128.84, 128.02, 46.62, 37.35; LCMS (m/z): 403.26(M+H);. Molecular formula: C₁₇H₁₄N₄O₄S₂; Elemental analysis: Calculated: C-50.74, H-3.51, N-13.92. Obtained: C-50.68, H-3.49, N-13.98.

3. BIOLOGICAL ACTIVITY:

Anti-Bacterial Activity:

The anti-bacterial activities of newly synthesized compounds are examined against 5 pathogenic bacteria strains. The result of antibiotic activity studies for the compounds. The gram negative bacteria screened were *Escherichia Coli* NCCS 2065 and *Pseudomonas aeruginosa* NCS 2200. The gram positive bacteria screened were *S-aureas* NCCS 2079 and *Bacillus* NCCS 2106.

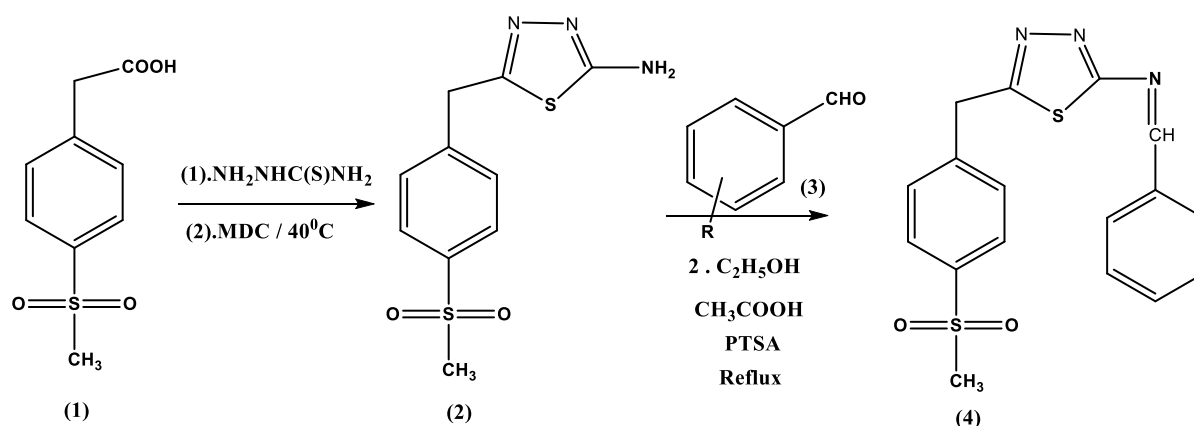
The target compounds were used at the concentration of 250 µg/ml and 500 µg/ml using DMSO as a solvent the amoxylin 10 µg/ml disc were used as a standard. The rest of the compounds were found to be moderate active against the tested microorganism

Anti-Fungal Activity:

Anti-fungal activity of new synthesized compounds were examined by disc diffusion method against the organism of *aspergillusniger* NCCS 1196 and *Candida ablicans* NCCS 3471. Compared were treated at the concentrations of 500 µg/ml and 1000 µg/ml using DMSO as a solvent. The standard drug was used as ketoconazol 50 µg/ml against both organisms.

4. RESULT AND DISCUSSIONS:

In this investigation, the synthesis of novel N-(5-(4-(methylsulfonyl) benzyl)-1, 3, 4-thiadiazol-2-yl)-1-phenylmethanimine was mediated by P-Toluene Sulphonic acid is a three-component reaction of 5-(4-(methylsulfonyl) benzyl)-1, 3, 4-thiadiazol-2-amine with substituted aromatic aldehyde in acetonitrile at reflux. The compound 5-(4-(methylsulfonyl) benzyl)-1, 3, 4-thiadiazol-2-amine is obtained from 2-(4-(methylsulfonyl) phenyl) acetic acid and thiosemicarbazide taken in con H_2SO_4 in DMF as solvent at 70-80°C. The result and discussion of titled derivatives as followed



(Scheme -1)

Overall the reaction, we observed that the yield obtained during synthesis, the derivatives bearing electron attracting group lower product than the derivatives having electron releasing group bearing including the halogen containing group also got excellent yield. The advantages of this catalyst, it was commercially available, easy handling when it was applied into the reaction, short reaction time, and easy work up and an excellent product yields, easy to simple work-up procedure and titled products were purified by non-chromatographic process. The catalyst was played an important vital role during the synthesis until the reaction was completed. There are various PTSA were utilized as catalysts in this reaction. In this process, a variety of copper halides were used as catalysts, such as MSA, CSA, and SSA are the ones that can be added to boost the yield of desired compounds. The function of PTSA catalyst was used to obtained excellent yield. Table I illustrates how the derivatives' product reduces the usage of MSA, SSA, and CSA.

Table-I: The optimization of various PTSA catalysts for the synthesis of derivatives:

Entry	Catalyst	Yield (%)	Time(min)
1	MSA	58%	120
2	SSA	62%	120

3	PTSA	92%	120
4	CSA	75%	120

The progress of the reaction was observed when we were added catalyst in the reaction and we observed that there is no reaction progress, if the reaction started at room temperature in the absence of catalyst. After the catalyst was added in the reaction and then temperature gradually rises during reach at 75⁰C. We also recognized that the various molar ratio of catalyst was applied into the synthesis of titled derivatives at time of during the reaction. Finally, we observed that an increasing the amount of catalyst gradually during the reaction.

Initially, the reaction did not develop yield of product, after 20% product observed when slowly added the catalyst such as 0.5 mole and prolong improvement of yield when addition catalyst 1.0, 1.5 mole. An excellent outcome to afford the titled derivatives is 92% yield was obtained after addition of 2.0 mole catalyst. Further, there no improvement when added excess of amount of catalyst as shown in table-II

Table-II: Screening of the catalytic using loaded catalyst accountable for the synthesis of derivatives (6i):

Entry	Loaded Catalyst	Yield (%)	Time(min)
1	1.0	20	120
2	1.5	40	120
3	2.0	92	120
4	2.5	92	120
5	3.0	92	120

The solvent is used to an important significant yield of titled product. During this reaction and the percentage of titled derivatives mainly depend on the solubility of the reactants. There are different types of solvent applied in this synthesis such as polar solvent and non-polar solvent. The most suitable solvent is acetonitrile compared to other solvents. Use of polar protic and polar aprotic solvents in this process, including DMF, Acetonitrile, Ethanol, and Methanol, we found that acetonitrile is the most reliable and

efficient solvent. The rest of the solvents are not much affecting this synthesis such as decreases yield and expensive time factor. The excellent yield obtained in short reaction time when use as catalyst is PTSA.

Table-III: Screening of the catalytic uses various solvents accountable for the synthesis of derivatives:

Entry	Solvent	Yield (%)	Time(min)
1	DMF	50	120
2	Acetonitrile	92	120
3	Ethanol	76	120
4	Methanol	69	120

Antibacterial activity:

The standard "streptomycin" as standard drug was compared with the *in vitro* bactericidal activity of the named derivatives (4a-4f). The majority of the synthesized derivatives were usually rated as having potent activity against bacterial strains, as shown in Table IV. These findings reveals that the comparison to derivatives with electron withdrawing groups as well as derivatives with electron donating groups screened with moderate to good activity. The halogen-atom-containing analogous showed outstanding active potential against antibacterial activity.

Table-IV: - The invitro antibacterial, activities of Titled derivatives

Compound	Anti-Bacterial Activity			
	Gram(+ve) bacteria		Gram(-ve) bacteria	
	<i>Escherichia coli</i>	<i>P.aeruginosa</i>	<i>B. subtilis</i>	<i>S. aureus</i>
4a	08	08	09	07
4b	14	15	17	17
4c	21	20	22	22
4d	23	22	26	25
4e	11	10	09	06
4f	12	14	16	15
4g	10	08	12	14
streptomycin	27	27	30	30

The results of titled analogous was exhibited various values for in vitro antifungal activity such as *Aspergillus favus*, *Aspergillus Niger* and *Candida albicans* and indicated that the aromatic aldehydes were having a functional group that was reliant on the parent derivatives. Because they contain an electron-releasing moiety were exhibited an extraordinary potent activity. These weakly powerful activities were demonstrated by the derivatives which are having in the type of electron withdrawing nature. Table-V was provided a proof of this article's derivatives in shown given below.

Table-V: - The invitro antifungal activities of Titled derivatives:

Compound	Anti-Fungal Activity		
	<i>Aspergillus favus</i>	<i>Aspergillus Niger</i>	<i>Candida albicans</i>
4a	07	08	07
4b	12	14	12
4c	13	13	12
4d	17	15	17
4e	16	14	12
4f	10	12	11
4g	06	07	08
Ketonoazole	20	20	20

5. CONCLUSION:

The reaction condition carried out at room temperature for all the newly synthesised compounds. The yield of the titled compounds obtained from 85-92%.The compound possesses electron donating group gives maximum yield than that of the compound possesses electron withdrawing group. The rate of reaction developed by using MSA catalyst. All the compounds tested by anti-microbial activity against gram positive, gram negative and fungal. The compound having electron donating group showed excellent active potential .Otherwise the compounds having halogens which showed better active potential than that of the electron with drawing group.

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